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U.S. PATENT APPLICATION

FOR

NOVEL FLUTICASONE FORMULATIONS

BY

DOUGLAS HOVEY, TUULA RYDE, AND H. WILLIAM BOSCH

NOVEL FLUTICASONE FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Provisional Application No. 60/444,626, filed on February 4, 2003.

FIELD OF THE INVENTION

[0002] The present invention relates to a composition comprising fluticasone and at least one surface stabilizer.

BACKGROUND OF THE INVENTION

A. Background Regarding Nanoparticulate Compositions

[0003] Nanoparticulate compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles comprising a poorly soluble therapeutic or diagnostic agent having associated with the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of fluticasone.

[0004] Methods of making nanoparticulate compositions are described, for example, in U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

[0005] Nanoparticulate compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase

Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific

Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,428,814 for "Bioadhesive nanoparticulate compositions having cationic surface stabilizers;" 6,431,478 for "Small Scale Mill;" 6,432,381 for

"Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," 6,582,285 for "Apparatus for Sanitary Wet Milling," 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," and 6,656,504 for "Nanoparticulate Compositions Comprising Amorphous Cyclosporine and Methods of Making and Using Such Compositions," all of which are specifically incorporated by reference.

[0006] In addition, U.S. Patent Application No. 20020012675 A1, published on January 31, 2002, for "Controlled Release Nanoparticulate Compositions," and WO 02/098565 for "System and Method for Milling Materials," describe nanoparticulate active agent compositions, and are specifically incorporated by reference. None of these references describe nanoparticulate compositions of fluticasone.

[0007] Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

B. Background Regarding Fluticasone

[0008] Fluticasone propionate is a synthetic, trifluorinated, corticosteroid having the chemical name of S-fluoromethyl-6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate, and the empirical formula $C_{25}H_{31}F_3O_5S$. It is a white to off-white powder with a molecular weight of 500.6. Fluticasone propionate is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethyl-formamide, and slightly soluble in methanol and 95% ethanol.

[0009] Fluticasone propionate is described and claimed in British Patent No. 2088877. The compound has potent anti-inflammatory activity and is particularly useful for the treatment of respiratory disorders, particularly asthma. *In vitro* assays using human lung cytosol preparations have established fluticasone propionate as a human

glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, and almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of budesonide.

[0010] Depending on the mode of administration, fluticasone propionate can be used to treat, for example, respiratory related illnesses such as asthma, emphysema, respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), chronic bronchitus, cystic fibrosis, acquired immune deficiency syndrome, including AIDS related pneumonia, seasonal or perennial rhinitis, seasonal or perennial allergic and nonallergic (vasomotor) rhinitis, or skin conditions treatable with topical corticosteroids. Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties.

[0011] When administered in an aerosol, fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. *See Physicians' Desk Reference*, 57th Edition, pp. 1433 (Thompson PDR, NJ 2003). Studies using oral dosing of labeled and unlabeled conventional fluticasone propionate have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. *Id.*

[0012] The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. *Id.* at 1498.

[0013] Fluticasone propionate has been obtained in a crystalline form, designated Form 1, by dissolving the crude product (obtained, *e.g.* as described in British Patent No. 2088877) in ethyl acetate and then recrystallizing. Standard spray-drying techniques have also been shown to lead only to the known Form 1 of fluticasone propionate. *See* U.S. Patent No. 6,406,718 to Cooper et al. A second polymorphic form of fluticasone propionate, prepared using supercritical fluid technology, is described in Cooper et al.

[0014] Cooper et al. describe a method for forming a particulate fluticasone propionate product comprising the co-introduction of a supercritical fluid and a vehicle

containing at least fluticasone propionate in solution or suspension into a particle formation vessel, the temperature and pressure in which are controlled, such that dispersion and extraction of the vehicle occur substantially simultaneously by the action of the supercritical fluid. Chemicals described as being useful as supercritical fluids include carbon dioxide, nitrous oxide, sulphur hexafluoride, xenon, ethylene, chlorotrifluoromethane, ethane, and trifluoromethane. The supercritical fluid may optionally contain one or more modifiers, such as methanol, ethanol, ethyl acetate, acetone, acetonitrile or any mixture thereof. A supercritical fluid modifier (or co-solvent) is a chemical which, when added to a supercritical fluid, changes the intrinsic properties of the supercritical fluid in or around the critical point. According to Cooper et al., the fluticasone propionate particles produced using supercritical fluids have a particle size range of 1 to 10 microns, preferably 1 to 5 microns.

[0015] There are several disadvantages associated with the fluticasone compositions of Cooper et al. First, particle sizes of less than 1 micron are desirable, as smaller particle sizes can be associated with a more rapid dissolution upon administration, and consequent faster onset of action as well as greater bioavailability. Moreover, very small fluticasone particles, *i.e.,* less than about 150 nm in diameter, are desirable as such compositions can be sterile filtered. In addition, the fluticasone particles of Cooper et al. may comprise supercritical fluid residues, which are undesirable as they do not have pharmaceutical properties and they can potentially cause adverse reactions.

[0016] Fluticasone propionate is marketed in several different commercial forms. ADVAIR DISKUS® (GlaxoSmithKline, Research Triangle Park, NC) is an inhalation powder of a combination of microfine fluticasone propionate and salmeterol xinofoate, which is a highly selective $beta_2$-adrenergic bronchodilator. The dosage form is marketed in three doses of fluticasone propionate: 100 mcg, 250 mcg, and 500 mcg. Following administration of ADVAIR® DISKUS® to healthy subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours. *See Physicians' Desk Reference*, 57th Edition, pp. 1433 (Thompson PDR, NJ 2003). Upon administration of ADVAIR® DISKUS® 500/50 (containing 500 mcg fluticasone propionate and 50 mcg salmeterol xinofoate), fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given

concurrently, or fluticasone propionate powder 500 mcg alone, mean peak steady-state plasma concentrations of fluticasone propionate averaged 57, 73, and 70 pg/mL, respectively. *Id.* Peak steady-state fluticasone propionate plasma concentration in adult patients (n = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS® device. The mean fluticasone propionate plasma concentration was 110 pg/mL. The systemic bioavailability of fluticasone propionate inhalation powder using the DISKUS® device in healthy volunteers averages 18%. *Id.* ADVAIR DISKUS® is indicated for the long-term, twice-daily, maintenance treatment of asthma. *Id.* at 1435.

[0017] FLOVENT® DISKUS® (GlaxoSmithKline) is an oral inhalation powder of microfine fluticasone propionate (50 mcg, 100 mcg, and 250 mcg) in lactose. *Id.* at 1526. Under standardized *in vitro* test conditions, FLOVENT® DISKUS® delivers 47, 94, or 235 mcg of fluticasone propionate from FLOVENT® DISKUS® 50 mcg, 100 mcg, and 250 mcg, respectively. *Id.* The systemic bioavailability of fluticasone propionate from the DISKUS® device in healthy adult volunteers averages about 18%. FLOVENT® DISKUS® is indicated for the maintenance treatment of asthma as prophylactic therapy, and for patients requiring oral corticosteroid therapy for asthma. *Id.* at 1527.

[0018] FLOVENT® ROTADISK® (GlaxoSmithKline) is an oral inhalation powder of microfine fluticasone propionate (50 mcg, 100 mcg, and 250 mcg) blended with lactose. *Id.* at 1530. Under standardized *in vitro* test conditions, FLOVENT® ROTADISK® delivers 44, 88, or 220 mcg of fluticasone propionate from FLOVENT® ROTADISK® 50 mcg, 100 mcg, or 250 mcg, respectively. *Id.* The systemic bioavailability of fluticasone propionate from the ROTADISK® device in healthy adult volunteers averages about 13.5%. *Id.* FLOVENT® ROTADISK® is indicated for the maintenance treatment of asthma as prophylactic therapy, and for patients requiring oral corticosteroid therapy for asthma. *Id.* at 1531.

[0019] FLOVENT® (GlaxoSmithKline) is an oral inhalation aerosol of a microcrystalline suspension of fluticasone propionate (44 mcg, 110 mcg, or 220 mcg) in a mixture of two chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with lecithin. Each actuation of the inhaler delivers 50, 125, or

250 mcg of fluticasone propionate from the valve, and 44, 110, or 220 mcg, respectively, of fluticasone propionate from the actuator. *Id.* at 1523. The systemic bioavailability of fluticasone propionate inhalation aerosol in healthy volunteers averages about 30% of the dose delivered from the actuator. Peak plasma concentrations after an 880-mcg inhaled dose ranged from 0.1 to 1.0 ng/mL. *Id.* FLOVENT® is indicated for the maintenance treatment of asthma as prophylactic therapy. *Id.* at 1524.

[0020] FLONASE® (GlaxoSmithKline) is a nasal spray of an aqueous suspension of microfine fluticasone propionate (50 mcg) administered by means of a metering, atomizing spray pump. *Id.* at 1521. The dosage form also contains microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol. *Id.* Indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. *Id.* After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (50 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. *Id.* Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral dosing of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is neglible, and the majority of the circulating radioactivity is due to an inactive metabolite. *Id.* Studies comparing the effect of oral and nasal dosing demonstrate that the therapeutic effect of FLONASE® can be attributed to the topical effects of fluticasone propionate applied to the nasal mucosa. *Id.* FLONASE® nasal spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis. *Id.* at 1522.

[0021] CUTIVATE® (GlaxoSmithKline) is a topical dermatological fluticasone propionate cream or ointment (0.05% and 0.005% concentration). The cream and ointment are a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. *Id.* at 1498. In a human study of 12 healthy males receiving 12.5 g of 0.05% fluticasone propionate cream

twice daily for 3 weeks, plasma levels were generally below the level of quantification (0.05 ng/mL). In another study of 6 healthy males administered 25 g of 0.05% fluticasone propionate cream under occlusion for 5 days, plasma levels of fluticasone ranged from 0.07 to 0.39 ng/mL. *Id.* at 1496. In a study of 6 healthy volunteers applying 26 g of fluticasone propionate ointment 0.005% twice daily to the trunk and legs for up to 5 days under occlusion, plasma levels of fluticasone ranged from 0.08 to 0.22 ng/mL. *Id.*

[0022] Adverse reactions from the current marketed forms of fluticasone propionate include lymphatic signs and symptoms; cardiovascular palpitations; hypersensitivity reactions, including agioedema, skin rash, edema of the face and tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions; otitis media; tonsillitis; rhinorrhea/postnasal drip/nasal discharge; earache; cough; laryngitis; hoarseness/dysphonia; epistaxis; tonsillitis; nasal signs and symptoms; unspecified oropharyngeal plaques; ear, nose, and throat polyps; sneezing; pain in nasal sinuses; rhinitis; throat constriction; allergic ear, nose, and throat disorders; alteration or loss of sense of taste and/or smell; nasal septal perforation; blood in nasal mucosa; nasal ulcer; voice changes; fluid disturbances; weight gain; goiter; disorders of uric acid metabolism; appetite disturbances; irritation of the eyes; blurred vision; glaucoma; increased intraocular pressure and cataracts; keratitis and conjunctivitis; blepharoconjunctivitis; nausea and vomiting; abdominal pain; viral gastroenteritis; gastroenteritis/colitis; gastrointestinal infections; abdominal discomfort; diarrhea; constipation; appendicitis; dyspepsia and stomach disorder; abnormal liver function; injury; fever; tooth decay; dental problems; mouth irritation; mouth and tongue disorders; cholecystitis; lower respiratory infections; pneumonia; arthralgia and articular rheumatism; muscle cramps and spasms; fractures; wounds and lacerations; contusions and hematomas; burns; musculoskeletal inflammation; bone and cartilage disorders; pain in joint; sprain/strain; disorder/symptoms of neck; muscular soreness/pain; aches and pains; pain in limb; dizziness/giddiness; tremors; hypnagogic effects; compressed nerve syndromes; sleep disorders; paralysis of cranial nerves; migraine; nervousness; bronchitis; chest congestion and/or symptoms; malaise and fatigue; pain; edema and swelling; bacterial infections; fungal infections; mobility disorders; cysts, lumps, and masses; mood

disorders; acute nasopharyngitis; dyspnea; irritation due to inhalant; urticaria; rash/skin eruption; disorders of sweat and sebum; sweating; photodermatitis; dermatitis and dermatosis; viral skin infections; eczema; fungal skin infections; pruritus; acne and folliculitis; burning; hypertrichosis; increased erythema; hives; folliculitis; hypopigmentation; perioral dermatitis; skin atrophy; striae; miliaria; pustular psoriasis; urinary infections; bacterial reproductive infections; dysmenorrhea; candidiasis of vagina; pelvic inflammatory disease; vaginitis/vulvovaginitis; and irregular menstrual cycle. *Id.* at 1438, 1498-99, 1523, 1525, 1529, and 1532.

[0023] There is a need in the art for fluticasone formulations which can decrease frequency of dosing, improve clinical efficacy, and potentially reduce side effects. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

[0024] The present invention relates to compositions comprising fluticasone and at least one surface stabilizer. The fluticasone particles in the composition may have an effective average particle size of less than about 2000 nm.

[0025] Another aspect of the invention is directed to pharmaceutical compositions comprising a fluticasone composition of the invention. The pharmaceutical compositions preferably comprise fluticasone, at least one surface stabilizer, and at least one pharmaceutically acceptable carrier, as well as any desired excipients.

[0026] Moreover, the invention is directed to fluticasone compositions which can be sterile filtered.

[0027] In yet another embodiment, the invention is directed to bioadhesive fluticasone formulations. Such compositions are useful, for example, for oral, nasal, or topical applications.

[0028] This invention further discloses a method of making a fluticasone composition. Such a method comprises contacting fluticasone and at least one surface stabilizer for a time and under conditions sufficient to provide a fluticasone composition in which the fluticasone particles have an effective average particle size of less than about

2 microns. The one or more surface stabilizers can be contacted with fluticasone either before, during, or after size reduction of the fluticasone.

[0029] Finally, the invention is directed to methods of treatment using the fluticasone compositions of the invention.

[0030] Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0031] The present invention is directed to compositions comprising fluticasone and at least one surface stabilizer. The fluticasone particles in the composition may have an effective average particle size of less than about 2000 nm.

[0032] As taught in the '684 patent, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. It was surprisingly discovered that stable nanoparticulate fluticasone formulations can be made.

[0033] The current formulations of fluticasone for oral, nasal, or topical administration suffer from the following problems: (1) the poor solubility of the drug necessitates making a suspension in water or a dry powder for oral or nasal administration; (2) dosing must be repeated several times each day; (3) poor bioavailability; and (4) a wide variety of side effects are associated with the current fluticasone dosage forms.

[0034] The present invention overcomes problems encountered with the prior art fluticasone formulations. Specifically, the fluticasone compositions of the invention may offer the following advantages: (1) the composition may be formulated as a ready to use colloidal dispersion rather than as a suspension that may settle or must be prepared immediately before dosing; (2) the composition can be formulated in a dried form which readily redisperses; (3) the composition may offer a potential decrease in the frequency of dosing; (4) smaller doses of drug may be required to obtain the same pharmacological

effect as compared to conventional microcrystalline or soluble forms of fluticasone; (5) bioadhesive fluticasone compositions that can coat the nasal or pulmonary cavity, or the desired site of application for dermatological applications and be retained for a period of time, thereby increasing the efficacy of the drug as well as eliminating or decreasing the frequency of dosing; (6) nanoparticulate fluticasone formulations having very small particle sizes can be sterile filtered; and (7) the nanoparticulate fluticasone compositions of the invention do not require organic solvents or pH extremes.

[0035] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0036] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0037] As used herein with reference to stable drug particles, "stable" includes, but is not limited to, one or more of the following parameters: (1) that the fluticasone particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly increase in particle size over time; (2) that the physical structure of the fluticasone particles is not altered over time, such as by conversion from an amorphous phase to crystalline phase; (3) that the fluticasone particles are chemically stable; and/or (4) where the fluticasone has not been subject to a heating step at or above the melting point of the fluticasone in the preparation of the nanoparticles of the invention.

[0038] "Conventional active agents or drugs" refers to non-nanoparticulate compositions of active agents or solubilized active agents or drugs. Non-nanoparticulate active agents have an effective average particle size of greater than about 2 microns, meaning that at least 50% of the active agent particles have a size greater than about 2 microns. (Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2 microns.)

[0039] "Pharmaceutically acceptable" as used herein refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound

medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0040] "Pharmaceutically acceptable salts" as used herein refers to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[0041] "Therapeutically effective amount" as used herein with respect to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that 'therapeutically effective amount,' administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "therapeutically effective amount" by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

A. Preferred Characteristics of the Nanoparticulate Fluticasone Compositions of the Invention

1. Lower Doses and Frequency of Dosing Offered by the Fluticasone Compositions of the Invention

[0042] Conventional fluticasone formulations used in treating nasal or respiratory conditions are generally dosed one inhalation twice daily (for ADVAIR® DISKUS®, FLOVENT®, FLOVENT® DISKUS®, and FLOVENT® ROTADISK®, at all three strengths;), at regular intervals as needed (FLONASE®), or a thin film of CULTIVATE® cream or ointment once or twice daily. *See Physicians' Desk Reference*, 57th Edition, pp. 1438, 1497, 1499, 1522, 1525, 1528, and 1532 (2003).

[0043] In contrast, the fluticasone compositions of the invention can be administered less frequently and at lower doses than the currently marketed forms of fluticasone. Lower dosages can be used because the small particle size of the fluticasone particles ensure greater absorption, and in the case of bioadhesive nanoparticulate fluticasone compositions, the fluticasone is retained at the desired site of application for a longer period of time as compared to conventional fluticasone dosage forms, thereby increasing the effectiveness of the dosage form.

2. Bioadhesive Fluticasone Compositions

[0044] The invention is also directed to bioadhesive fluticasone formulations for oral, nasal, or topical application. Bioadhesive formulations of the invention are primarily useful in cutaneous, oral (including pulmonary), and nasal applications. Bioadhesive nanoparticulate compositions were first described in U.S. Patent No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers."

[0045] Bioadhesive fluticasone compositions comprise fluticasone particles and at least one cationic surface stabilizer. The fluticasone particles can have an effective average particle size of less than about 2 microns. The composition may also comprise one or more secondary surface stabilizers, which can be non-cationic.

[0046] Bioadhesive formulations of fluticasone exhibit exceptional bioadhesion to biological surfaces, such as hair, mucous, skin, *etc.* The term bioadhesion refers to any

attractive interaction between two biological surfaces or between a biological and a synthetic surface. In the case of bioadhesive fluticasone compositions of the invention, the term bioadhesion is used to describe the adhesion between the fluticasone compositions and a biological substrate (*i.e.* gastrointestinal mucin, lung tissue, nasal mucosa, skin, *etc.*). There are basically two mechanisms which may be responsible for this bioadhesion phenomena: mechanical or physical interactions and chemical interactions. The first of these, mechanical or physical mechanisms, involves the physical interlocking or interpenetration between a bioadhesive entity and the receptor tissue, resulting from a good wetting of the bioadhesive surface, swelling of the bioadhesive polymer, penetration of the bioadhesive entity into a crevice of the tissue surface, or interpenetration of bioadhesive composition chains with those of the mucous or other such related tissues. The second possible mechanism of bioadhesion, chemical, incorporates strong primary bonds (*i.e.*, covalent bonds) as well as weaker secondary forces such as ionic attraction, van der Waals interactions, and hydrogen bonds. It is believed that this chemical form of bioadhesion is primarily responsible for the bioadhesive properties of the fluticasone compositions described herein. However, physical and mechanical interactions may also play a secondary role in the bioadhesion of such fluticasone compositions.

[0047] Because of the character of biological surfaces, the cationic surface stabilizers of the invention result in bioadhesive formulations. Surprisingly, the bioadhesive property of nanoparticulate active agent compositions comprising cationic surface stabilizers diminishes as the particle size of the active agent increases, as noted in U.S. Patent No. 6,428,814.

[0048] The bioadhesive fluticasone compositions are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive fluticasone compositions of the invention coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.

[0049] The adhesion exhibited by the inventive compositions means that fluticasone particles are not easily washed off, rubbed off, or otherwise removed from the biological surface for an extended period of time. The period of time in which a

biological cell surface is replaced is the factor that limits retention of the bioadhesive fluticasone particles to that biological surface. For example, skin cells are replaced every 24-48 hours. Thus, the fluticasone composition would have to be reapplied to the skin every 48 hours. Mucous cells shed and are replaced about every 5-6 hours. Other biological surfaces, such as chitin, hair, teeth, and bone, do not routinely shed cells and, therefore, repeat applications may not be necessary.

[0050] Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, 1,2 Dipalmitoyl-sn-Glycero-3-Phosphoethanolamine-N-[Amino(Polyethylene Glycol)2000] (sodium salt) (also known as DPPE-PEG(2000)-Amine Na) (Avanti Polar Lipids, Alabaster, Al), Poly(2-methacryloxyethyl trimethylammonium bromide) (Polysciences, Inc., Warrington, PA) (also known as S1001), poloxamines such as Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.), lysozyme, long-chain polymers such as alginic acid, carrageenan (FMC Corp.), and POLYOX (Dow, Midland, MI).

[0051] Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride or bromide, N-alkyl

(C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

[0052] Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants:*

Analytical and Biological Evaluation (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

[0053] Nonpolymeric cationic surface stabilizers are any nonpolymeric compound, such as benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

(viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

(ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

(x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

(xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

(xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

[0054] Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

[0055] Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

3. Sterile Filterable Nanoparticulate Fluticasone Compositions

[0056] According to the invention, a sterile filtered fluticasone composition may comprise: (1) fluticasone particles having an effective average particle size of less than about 200 nm, and (2) at least one surface stabilizer. Two or more surface stabilizers may be used in combination.

[0057] In other embodiments of the invention, the sterile filterable nanoparticulate fluticasone compositions have an effective average particle size of less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100 nm, less than about 90 nm, less than about 80 nm, less than about 70 nm, less

than about 60 nm, or less than about 50 nm. Because the compositions have such a small effective average particle size, they can be readily sterile filtered.

[0058] In preferred embodiments of the invention, at least about 99.9% of the fluticasone particles have an effective average particle size of less than 200 nm (D99), or at least about 90% of the fluticasone particles having an effective average particle size of less than 130 nm (D90).

[0059] Filtration is a highly cost-effective method for sterilizing homogeneous solutions when the membrane filter pore size is less than or equal to about 0.2 microns (200 nm) because a 0.2 micron filter is sufficient to remove essentially all bacteria. Sterile filtration, in addition to being cost effective, has other advantages in that certain compounds are not able to be sterilized by other methods, such as heat or gamma irradiation.

[0060] Sterile filtration is normally not used to sterilize conventional suspensions of micron-sized drug particles because the drug particles are too large to pass through the membrane pores. In principle, 0.2 μm filtration can be used to sterilize nanoparticulate active agent compositions. However, because nanoparticulate active agent compositions have a *size range*, many of the particles of a typical nanoparticulate active agent composition having an average particle size of 200 nm may have a size greater than 200 nm. Such larger particles tend to clog the sterile filter. Thus, only nanoparticulate active agent compositions having very small average particle sizes can be sterile filtered.

[0061] The U.S. Food and Drug Administration has recently issued guidelines requiring aqueous orally inhaled products to be sterile. This is problematic for aerosol formulations of nanoparticulate drugs, as heat sterilization can result in crystal growth and particle aggregation of such formulations, and sterile filtration can be difficult because of the required small particle size of the composition.

[0062] Administration by inhalation of corticosteroids, compared with oral administration, is preferable as this mode of administration reduces the risk of systemic side effects. The reduced risk of side effect arises from the mode of administration because corticosteroids are highly active topically and only weakly active systemically, thereby minimizing effects on the pituitary-adrenal axis, the skin, and the eye. Side

effects associated with inhalation therapy are primarily oropharyngeal candidiasis and dysphonia (due to atrophy of laryngeal muscles). Oral corticosteroids cause atrophy of the dermis with thin skin, striae, and ecchymoses but inhaled corticosteroids do not cause similar changes in the respiratory tract.

[0063] Other advantages of inhaled over oral administration include direct deposition of steroid in the airways which generally provides more predictable administration. The oral doses required for adequate control vary substantially, whereas inhaled corticosteroids are usually effective within a narrower range. There are, however, a number of factors that influence the availability of inhaled corticosteroids: extent of airway inflammation, degree of lung metabolism, amount of drug swallowed and metabolized in the gastrointestinal tract, the patient's ability to coordinate the release and inspiration of the medication, type of corticosteroid, and the delivery system.

[0064] A sterile inhaled fluticasone dosage form is particularly useful in treating immunocompromised patients, infants or juvenile patients, and the elderly, as these patient groups are the most susceptible to infection caused by a non-sterile fluticasone dosage form.

4. Low Viscosity Liquid Dosage Forms

[0065] A liquid dosage form of a conventional microcrystalline or non-nanoparticulate fluticasone composition would be expected to be a relatively large volume, highly viscous substance which would not be well accepted by patient populations. Moreover, viscous solutions can be problematic in parenteral and aerosol administration because these solutions require a slow syringe push and can stick to tubing. In addition, conventional formulations of poorly water-soluble active agents, such as fluticasone, tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with highly water-soluble substances.

[0066] Liquid dosage forms of the nanoparticulate fluticasone compositions of the invention provide significant advantages over a liquid dosage form of a conventional fluticasone microcrystalline compound. The low viscosity and silky texture of liquid dosage forms of the nanoparticulate fluticasone compositions of the invention result in

advantages in both preparation and use. These advantages include, for example: (1) better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (2) ease of dispensing because one can use a cup or a syringe; (3) potential for formulating a higher concentration of fluticasone resulting in a smaller dosage volume and thus less volume for the subject to consume; and (4) easier overall formulation concerns.

[0067] Liquid fluticasone dosage forms which are easier to consume are especially important when considering juvenile patients, terminally ill patients, and elderly patients. Viscous or gritty formulations, and those that require a relatively large dosage volume, are not well tolerated by these patient populations. Liquid oral dosage forms can be particularly preferably for patient populations who have difficulty consuming tablets, such as infants and the elderly.

[0068] The viscosities of liquid dosage forms of nanoparticulate fluticasone according to the invention are preferably less than about 1/200, less than about 1/175, less than about 1/150, less than about 1/125, less than about 1/100, less than about 1/75, less than about 1/50, or less than about 1/25 of a liquid oral dosage form of a conventional, non-nanoparticulate fluticasone composition, at about the same concentration per ml of fluticasone.

[0069] Typically the viscosity of liquid nanoparticulate fluticasone dosage forms of the invention, at a shear rate of 0.1 (1/s), is from about 2000 mPa s to about 1 mPa s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100

mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, or from about 5 mPa·s to about 1 mPa·s. Such a viscosity is much more attractive for subject consumption and may lead to better overall subject compliance.

[0070] Viscosity is concentration and temperature dependent. Typically, a higher concentration results in a higher viscosity, while a higher temperature results in a lower viscosity. Viscosity as defined above refers to measurements taken at about 20°C. (The viscosity of water at 20°C is 1 mPa s.) The invention encompasses equivalent viscosities measured at different temperatures.

[0071] Another important aspect of the invention is that the nanoparticulate fluticasone compositions of the invention are not turbid. "Turbid," as used herein refers to the property of particulate matter that can be seen with the naked eye or that which can be felt as "gritty." The nanoparticulate fluticasone compositions of the invention can be poured out of or extracted from a container as easily as water, whereas a liquid dosage form of a non-nanoparticulate or solubilized fluticasone is expected to exhibit notably more "sluggish" characteristics.

[0072] The liquid formulations of this invention can be formulated for dosages in any volume but preferably equivalent or smaller volumes than a liquid dosage form of a conventional non-nanoparticulate fluticasone composition.

5. Redispersibility Profiles of Solid Dose Forms of the Nanoparticulate Fluticasone Compositions of the Invention

[0073] An additional feature of solid dose forms of the nanoparticulate fluticasone compositions of the invention, such as dry powder aerosols, is that the dosage forms redisperse such that the effective average particle size of the redispersed fluticasone particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate fluticasone particles present in the compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating fluticasone into a nanoparticulate particle size.

[0074] This is because nanoparticulate fluticasone compositions benefit from the small particle size of fluticasone; if the nanoparticulate fluticasone particles do not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated fluticasone particles are formed. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

[0075] Moreover, solid dose forms of the nanoparticulate fluticasone compositions of the invention exhibit dramatic redispersion of the nanoparticulate fluticasone particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution in a biorelevant aqueous media. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

[0076] Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. *See e.g.*, Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res., 14* (4): 497-502 (1997).

[0077] It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, *etc.*

[0078] Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For

example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less, about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

[0079] Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

[0080] Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

[0081] In other embodiments of the invention, the redispersed fluticasone particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable media) have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0082] Redispersibility can be tested using any suitable means known in the art. *See e.g.*, the example sections of U.S. Patent No. 6,375,986 for "Solid Dose

Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

6. Combination Active Agent Compositions

[0083] The invention encompasses the nanoparticulate fluticasone compositions of the invention formulated or co-administered with one or more non-fluticasone active agents, which are either conventional (solubilized or microparticulate) or nanoparticulate. Methods of using such combination compositions are also encompassed by the invention. The non-fluticasone active agents can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

[0084] The compound to be administered in combination with a nanoparticulate fluticasone composition of the invention can be formulated separately from the nanoparticulate fluticasone composition or co-formulated with the nanoparticulate fluticasone composition. Where a nanoparticulate fluticasone composition is co-formulated with a second active agent, the second active agent can be formulated in any suitable manner, such as immediate-release, rapid-onset, sustained-release, or dual-release form.

[0085] If the non-fluticasone active agent has a nanoparticulate particle size *i.e.*, a particle size of less than about 2 microns, then preferably it will have one or more surface stabilizers associated with the surface of the active agent. In addition, if the active agent has a nanoparticulate particle size, then it is preferably poorly soluble and dispersible in at least one liquid dispersion media. By "poorly soluble" it is meant that the active agent has a solubility in a liquid dispersion media of less than about 30 mg/mL, less than about 20 mg/mL, less than about 10 mg/mL, or less than about 1 mg/mL. Useful liquid dispersion medias include, but are not limited to, water, aqueous salt solutions, safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol.

[0086] Such non-fluticasone active agents can be, for example, a therapeutic agent. A therapeutic agent can be a pharmaceutical agent, including biologics. The active agent can be selected from a variety of known classes of drugs, including, for example, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system

stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, such as NSAIDs and COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives (hypnotics and neuroleptics), astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

[0087] A description of these classes of active agents and a listing of species within each class can be found in Martindale's *The Extra Pharmacopoeia,* 31st Edition (The Pharmaceutical Press, London, 1996), specifically incorporated by reference. The active agents are commercially available and/or can be prepared by techniques known in the art.

[0088] Exemplary nutraceuticals and dietary supplements are disclosed, for example, in Roberts et al., *Nutraceuticals: The Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods* (American Nutraceutical Association, 2001), which is specifically incorporated by reference. Dietary supplements and nutraceuticals are also disclosed in *Physicians' Desk Reference for Nutritional Supplements*, 1st Ed. (2001) and *The Physicians' Desk Reference for Herbal Medicines,* 1st Ed. (2001), both of which are also incorporated by reference. A nutraceutical or dietary supplement, also known as a phytochemical or functional food, is generally any one of a class of dietary supplements, vitamins, minerals, herbs, or healing foods that have medical or pharmaceutical effects on the body.

[0089] Exemplary nutraceuticals or dietary supplements include, but are not limited to, lutein, folic acid, fatty acids (*e.g.*, DHA and ARA), fruit and vegetable extracts, vitamin and mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids (*e.g.*, arginine, isoleucine, leucine, lysine, methionine, phenylanine, threonine, tryptophan, and valine), green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics. Nutraceuticals and dietary supplements also include bio-engineered foods genetically engineered to have a desired property, also known as "pharmafoods."

B. Fluticasone Compositions

[0090] The invention provides compositions comprising fluticasone particles and at least one surface stabilizer. The surface stabilizers adsorb to or associate with the surface of the fluticasone particles. Surface stabilizers useful herein do not chemically react with the fluticasone particles or itself. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages. The compositions can comprise two or more surface stabilizers.

[0091] The present invention also includes fluticasone compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers.

[0092] The fluticasone compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration (in solid, liquid, or aerosol (*i.e.*, pulmonary) form), vaginal, nasal, rectal, ocular, local (powders, creams, ointments or drops), buccal, intracisternal, intraperitoneal, topical administration, and the like. Exemplary fluticasone dosage forms of the invention include, but are not limited to, liquid dispersions, gels, powders, sprays, solid re-dispersable dosage forms, ointments, creams, aerosols (pulmonary and nasal), solid dose forms, *etc.*

1. Fluticasone Particles

[0093] As used herein the term fluticasone refers to the synthetic, trifluorinated, corticosteroid having the chemical name of S-fluoromethyl-6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate, and salts and derivatives thereof. "Fluticasone" as used in this invention encompasses fluticasone propionate as well as other forms of fluticasone.

[0094] Fluticasone propionate is a white to off-white powder, with the empirical formula $C_{25}H_{31}F_3O_5S$ and a molecular weight of 500.6. Fluticasone propionate is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

[0095] The fluticasone of the invention can be in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

[0096] Fluticasone propionate has potent anti-inflammatory activity and is particularly useful for the treatment of inflammatory or obstructive airway disorders. Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties.

2. Surface Stabilizers

[0097] The choice of a surface stabilizer for fluticasone is non-trivial and required extensive experimentation to realize a desirable formulation.

[0098] Combinations of more than one surface stabilizer can be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients, such as ionic, non-ionic, anionic, and zwitterionic surfactants. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Preferred surface stabilizers include non-ionic surfactants such as tyloxapol.

[0099] Depending upon the desired method of administration, bioadhesive formulations of fluticasone can be prepared by selecting one or more cationic surface stabilizers that impart bioadhesive properties to the resultant composition. Useful cationic surface stabilizers are described above.

[0100] Representative examples of other useful surface stabilizers include hypromellose (previously known as hydroxypropyl methylcellulose or HPMC), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.*, Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-lOG® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-

derivatized phospholipid, PEG-derivatized cholesterol, PEG- derivatized cholesterol derivative, PEG-derivatized vitamin A, PEG-derivatized vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

[0101] The surface stabilizers described herein are commercially available and/or can be prepared by techniques known in the art. Most of the surface stabilizers are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

3. Other Pharmaceutical Excipients

[0102] Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

[0103] Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

[0104] Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

[0105] Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

[0106] Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

[0107] Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

[0108] Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

[0109] Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

4. Fluticasone Particle Size

[0110] The compositions of the invention comprise fluticasone particles which preferably have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns), less than about 1900 nm, less than less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100 nm, less than about 90 nm, less than about 80 nm, less than about 70 nm, less than about 60 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0111] If the nanoparticulate fluticasone composition additionally comprises one or more non-fluticasone nanoparticulate active agents, then such active agents have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns). In other embodiments of the invention, the nanoparticulate non-fluticasone active agents can have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by the above-noted techniques.

[0112] By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the nanoparticulate fluticasone particles or nanoparticulate non-fluticasone active agent particles have a particle size of less than about 2000 nm, when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 99%, or at least about 99.9% of the nanoparticulate fluticasone particles or nanoparticulate non-fluticasone active agent particles have a particle size of less than the effective average, by weight, *i.e.*, less than about 2000 nm, less than about 1900 nm, less than less than about 1800 nm, less than about 1700 nm, *etc.*

[0113] If the nanoparticulate fluticasone composition is combined with a conventional or microparticulate fluticasone composition or non-fluticasone active agent composition, then such a composition is either solubilized or has an effective average particle size of greater than about 2 microns. By "an effective average particle size of greater than about 2 microns" it is meant that at least 50% of the conventional fluticasone or conventional non-fluticasone active agent particles have a particle size of greater than about 2 microns, by weight, when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 99%, or at least about 99.9%, by weight, of the

conventional fluticasone or conventional non-fluticasone active agent particles have a particle size greater than about 2 microns.

[0114] In the present invention, the value for D50 of a nanoparticulate fluticasone composition is the particle size below which 50% of the fluticasone particles fall, by weight. Similarly, D90 is the particle size below which 90% of the fluticasone particles fall, by weight.

5. Concentration of Fluticasone and Surface Stabilizers

[0115] The relative amounts of fluticasone and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, upon the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the surface stabilizer, *etc.*

[0116] The concentration of fluticasone can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined dry weight of the fluticasone and at least one surface stabilizer, not including other excipients.

[0117] The concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the fluticasone and at least one surface stabilizer, not including other excipients.

B. Methods of Making Nanoparticulate Fluticasone Formulations

[0118] The fluticasone compositions of the invention can be made using, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in the '684 patent. Methods of making nanoparticulate compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate

Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

[0119] The resultant nanoparticulate fluticasone compositions can be utilized in solid, semi-solid, or liquid dosage formulations, such as controlled release formulations, solid dose fast melt formulations, aerosol formulations, nasal formulations, lyophilized formulations, tablets, capsules, solid lozenge, powders, creams, ointments, *etc.*

1. Milling to Obtain Nanoparticulate Fluticasone Dispersions

[0120] Milling fluticasone to obtain a nanoparticulate fluticasone dispersion comprises dispersing fluticasone particles in a liquid dispersion medium in which fluticasone is poorly soluble, followed by applying mechanical means in the presence of grinding media, which is preferably less than about 500 micrometers in size, to reduce the particle size of fluticasone to the desired effective average particle size. The dispersion media can be any media in which fluticasone is poorly soluble, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. Water is a preferred dispersion media.

[0121] The fluticasone particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the fluticasone particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the fluticasone/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

2. Precipitation to Obtain Nanoparticulate Fluticasone Compositions

[0122] Another method of forming the desired nanoparticulate fluticasone composition is by microprecipitation. This is a method of preparing stable dispersions of

poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving fluticasone in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

3. Homogenization to Obtain Nanoparticulate Fluticasone Compositions

[0123] Exemplary homogenization methods of preparing nanoparticulate active agent compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

[0124] Such a method comprises dispersing fluticasone particles in a liquid dispersion medium in which fluticasone is poorly soluble, followed by subjecting the dispersion to homogenization to reduce the particle size of the fluticasone to the desired effective average particle size. The fluticasone particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the fluticasone particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the fluticasone/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

C. Methods of Treatment Using the Fluticasone Compositions of the Invention

[0125] The present invention is directed to methods of treating a subject in need using the fluticasone compositions of the invention.

[0126] As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

1. Methods and Fluticasone Dosage Forms of the Invention

[0127] The fluticasone compositions of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (*e.g.*, intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (*e.g.*, powders, ointments or drops), or as a buccal or nasal spray.

[0128] If the fluticasone compositions are formulated for aerosol inhalation, any suitable device can be used for administration of such a dosage form. Such devices are well known in the art.

[0129] Fluticasone compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include but are not limited to water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0130] The fluticasone compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[0131] Solid dosage forms for oral administration include, but are not limited to, gels, powders, capsules, tablets, pills, and granules. In such solid dosage forms, the active agent is usually admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or

extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0132] Liquid dosage forms for oral administration include pharmaceutically acceptable aerosols, emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active agent, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[0133] Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

2. Fluticasone Dosages

[0134] The method of the invention comprises administering to a subject an effective amount of a composition comprising fluticasone. Depending on the mode of administration, the fluticasone compositions of the invention are useful in treating any of the disorders mentioned herein.

[0135] 'Therapeutically effective amount' as used herein with respect to a fluticasone dosage, shall mean that dosage that provides the specific pharmacological

response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that 'therapeutically effective amount,' administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a 'therapeutically effective amount' by those skilled in the art. It is to be further understood that fluticasone dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

[0136] One of ordinary skill will appreciate that effective amounts of fluticasone can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of fluticasone in the compositions of the invention may be varied to obtain an amount of fluticasone that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered fluticasone, the desired duration of treatment, and other factors.

[0137] Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

3. Exemplary Disorders That Can be Treated with the Fluticasone Compositions of the Invention

[0138] The fluticasone compositions can be used for treating disorders such as respiratory related illnesses. Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable

include asthma of whatever type or genesis, including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, *e.g.* of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics (for convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome").

[0139] Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, *e.g.* of acute asthmatic or bronchoconstrictor attack, improvement in lung function, or improved airways hyperreactivity. It may further be evidenced by a reduced requirement for other, symptomatic therapy, *i.e.*, therapy for or intended to restrict or abort symptomatic attack when it occurs, for example, anti-inflammatory (*e.g.*, corticosteroid) or bronchodilatory.

[0140] Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome common to a substantial percentage of asthmatics and characterized by asthma attack, *e.g.*, between the hours of about 4 to 6 am, *i.e.*, at a time normally substantially distant from any previously administered symptomatic asthma therapy.

[0141] Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD, or COLD), including chronic bronchitis and emphysema, bronchiectasis, and exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis byssinosis. and inflammatory bowel diseases, including Crohn's disease and ulcerative colitis.

[0142] Other treatments may include Whipple's disease, AIDS related pneumonia, seasonal or perennial rhinitis, seasonal or perennial allergic an nonallergic (vasomotor) rhinitis, or skin conditions treatable with topical corticosteroids.

* * * * *

[0143] The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in this example. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

Example 1

[0144] The purpose of this example was to prepare a nanoparticulate dispersion of fluticasone propionate.

[0145] A mixture of 5% w/w fluticasone propionate (Abbott Laboratories, Abbott Park, IL) and 2.5% tyloxapol in saline was milled for 1.25 hours under high energy milling conditions in a DYNO®-Mill KDL (Willy A. Bachofen AG, Maschinenfabrik, Basel, Switzerland) equipped with a 150 cc batch chamber. 200 μm polymeric attrition media (The Dow Chemical Co., Midland, MI) was utilized in the milling process.

[0146] Particle size analysis of the milled fluticasone propionate composition, conducted using a Horiba LA-910 particle size analyzer (Irvine, CA) showed a final fluticasone propionate average particle size of 92 nm.

[0147] The composition was stable for at least 8 weeks at 5°C, 25°C, and 40°C.

Example 2

[0148] The purpose of this example was to prepare a sterile filtered nanoparticulate fluticasone propionate composition.

[0149] The milled fluticasone propionate composition of Example 1 was successfully sterile filtered using 0.8/0.2 micron syringe filters. The sterile filtered composition was stable for at least 8 weeks at 5°C, 25°C, and 40°C.

Example 3

[0150] The purpose of this example was to prepare a nanoparticulate dispersion of fluticasone propionate.

[0151] A mixture of 5% w/w fluticasone propionate and 2% tyloxapol in saline was milled for 40 min. under high energy milling conditions in a NanoMill® (Elan Drug Delivery, Inc.; *see* U.S. Patent No. 6,431,478) equipped with a 18 cc batch chamber. 200 μm polymeric attrition media (The Dow Chemical Co., Midland, MI) was utilized in the milling process.

[0152] Particle size analysis of the milled fluticasone propionate composition, conducted using a Horiba LA-910 particle size analyzer (Irvine, CA), showed a final fluticasone propionate mean particle size of 147 nm.

Example 4

[0153] The purpose of this example was to prepare a nanoparticulate dispersion of fluticasone propionate.

[0154] A mixture of 5% w/w fluticasone propionate and 2% poloxamer 338 in saline was milled for 60 min. under high energy milling conditions in a NanoMill® (Elan Drug Delivery, Inc.) equipped with a 18 cc batch chamber. 500 μm polymeric attrition media (The Dow Chemical Co., Midland, MI) was utilized in the milling process.

[0155] Particle size analysis of the milled fluticasone propionate composition, conducted using a Horiba LA-910 particle size analyzer (Irvine, CA), showed a final fluticasone propionate mean particle size of 153 nm.

Example 5

[0156] The purpose of this example was to prepare a nanoparticulate dispersion of fluticasone propionate.

[0157] An aqueous mixture of 5% w/w fluticasone propionate, 1% poloxamer 188, and 0.01% benzalkonium chloride was milled for 30 min. under high energy milling conditions in a NanoMill® (Elan Drug Delivery, Inc.) equipped with a 150 cc batch

chamber. 500 μm polymeric attrition media (The Dow Chemical Co., Midland, MI) was utilized in the milling process.

[0158] Particle size analysis of the milled fluticasone propionate composition, conducted using a Horiba LA-910 particle size analyzer (Irvine, CA), showed a final fluticasone propionate mean particle size of 381 nm.

Example 6

[0159] The purpose of this example was to prepare a nanoparticulate dispersion of fluticasone propionate.

[0160] An aqueous mixture of 5% w/w fluticasone propionate, 2% kollidon 17 PF, and 0.01% benzalkonium chloride was milled for 40 min. under high energy milling conditions in a NanoMill® (Elan Drug Delivery, Inc.) equipped with a 18 cc batch chamber. 500 μm polymeric attrition media (The Dow Chemical Co., Midland, MI) was utilized in the milling process.

[0161] Particle size analysis of the milled fluticasone propionate composition, conducted using a Horiba LA-910 particle size analyzer (Irvine, CA), showed a final fluticasone propionate mean particle size of 152 nm. Poor stability of the composition was observed at 5°C.

Example 7

[0162] The purpose of this example was to prepare a nanoparticulate dispersion of fluticasone propionate.

[0163] A mixture of 5% w/w fluticasone propionate and 2% lysozyme was milled for 30 min. under high energy milling conditions in a NanoMill® (Elan Drug Delivery, Inc.) equipped with a 18 cc batch chamber. 500 μm polymeric attrition media (The Dow Chemical Co., Midland, MI) was utilized in the milling process.

[0164] Particle size analysis of the milled fluticasone propionate composition, conducted using a Horiba LA-910 particle size analyzer (Irvine, CA), showed a final fluticasone propionate mean particle size of 311 nm.

Example 8

[0165] The purpose of this example was to prepare a nanoparticulate dispersion of fluticasone propionate.

[0166] A mixture of 5% w/w fluticasone propionate and 2% polysorbate 80 was milled for 40 min. under high energy milling conditions in a NanoMill® (Elan Drug Delivery, Inc.) equipped with a 18 cc batch chamber. 200 μm polymeric attrition media (The Dow Chemical Co., Midland, MI) was utilized in the milling process.

[0167] Particle size analysis of the milled fluticasone propionate composition, conducted using a Horiba LA-910 particle size analyzer (Irvine, CA), showed a final fluticasone propionate mean particle size of 115 nm. The composition showed poor stability at 5°C.

Example 9

[0168] The purpose of this example was to prepare a nanoparticulate dispersion of fluticasone propionate.

[0169] An aqueous mixture of 5% w/w fluticasone propionate, 1% hypromellose, and 0.01% benzalkonium chloride was milled under high energy milling conditions in a NanoMill® (Elan Drug Delivery, Inc.) equipped with a 18 cc batch chamber. 500 μm polymeric attrition media (The Dow Chemical Co., Midland, MI) was utilized in the milling process.

[0170] Particle size analysis of the milled fluticasone propionate composition could not be conducted due to the extremely large particle size. Large amounts of unmilled drug were seen in a photomicrograph.

Example 10

[0171] The purpose of this example was to prepare a nanoparticulate dispersion of fluticasone propionate, and to test the long term stability of the milled compositions.

[0172] A mixture of 5% w/w fluticasone propionate (Abbott Laboratories, Abbott Park, IL) and 2.5% tyloxapol in saline was milled for 1 hour under high energy milling conditions in a DYNO®-Mill KDL (Willy A. Bachofen AG, Maschinenfabrik, Basel,

Switzerland) equipped with a 150 cc batch chamber. 200 μm polymeric attrition media (The Dow Chemical Co., Midland, MI) was utilized in the milling process.

[0173] Particle size analysis of the milled fluticasone propionate composition, conducted using a Horiba LA-910 particle size analyzer (Irvine, CA) showed a final fluticasone propionate average particle size of 89 nm.

[0174] The fluticasone propionate dispersion was then diluted to 0.1% (w/w) fluticasone propionate and 0.05% (w/w) tyloxapol using saline and sterile filtered. The resultant formulation has been stable for at least 10 months at 5°C (with a mean particle size of 105 nm), 25°C (mean particle size of 111 nm), and 40°C (mean particle size of 144 nm).

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[0175] It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.